(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 November 2004 (11.11.2004)

PCT

(10) International Publication Number
WO 2004/096765 A2

(51) International Patent Classification[7]: C07D 209/00

(21) International Application Number:
PCT/IN2004/000121

(22) International Filing Date: 30 April 2004 (30.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
656/DEL/2003 1 May 2003 (01.05.2003) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A NOVEL CRYSTALLINE POLYMORPH OF FLUVASTATIN SODIUM AND A PROCESS FOR PREPARING IT

(57) Abstract: This invention relates to a novel crystalline polymorphic form BA of Fluvastatin Sodium and hydrates thereof, characterized by its IR and PXRD analysis. The invention also provides a process for the preparation of the novel polymorph that involves use of aliphatic ethers as antisolvent to facilitate precipitating. Further the addition of antisolvent is preferably carried out at a temperature above 40°C in the absence of seeding.

WO 2004/096765 A2

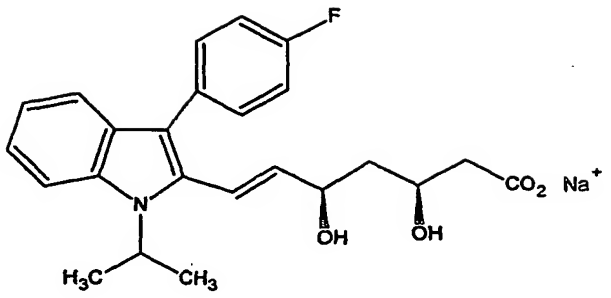
A NOVEL CRYSTALLINE POLYMORPH OF FLUVASTATIN SODIUM AND A PROCESS FOR PREPARING IT

FIELD OF THE INVENTION:

This invention relates to "A Novel Crystalline Polymorph of Fluvastatin Sodium and a Process for Preparing it". Particularly the invention relates to a novel crystalline polymorph of Fluvastatin Sodium having higher purity, stability, and solubility. The polymorph of the present invention contains up to 8% water content. The invention also provides a process, for the preparation of a novel polymorph, that is simple cost effective, reproducible, environment friendly easy to scale up for industrial manufacture without compromising the quality of the title product.

Fluvastatin is a member of the class of drug called statins. It is an inhibitor of 3-hydroxy-3-methyl glutaryl Coenzyme A (HMG – COA) and is used for the treatment of hyperlipidemia and hypocholesterolemia.

Fluvastatin Sodium is known by its chemical name as R*, S*-(E)-(±)-7-[3-(4-fluorophenyl)-1-(1-methyl ethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptanoic acid mono sodium salt. Fluvastatin Sodium is a racemic mixture of the 3R, 5S- and 3S, 5R-dihydroxy enantiomers. The empirical formula of Fluvastatin Sodium is $C_{24}H_{25}FNNaO_4$, molecular weight is 433.5 and it displays the following structural formula (1)



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Fluvastatin Sodium is a white to pale yellow amorphous or crystalline powder that is soluble in water & alcohol and pH of 1% solution in DM-Water is 8-10.

BACKGROUND Of THE INVENTION:

Fluvastatin as racemate well as its sodium salts are first disclosed in US Patent No. 4,739,073 and its EP equivalent EP patent no. 114027. Fluvastatin sodium is obtained in this patent by lyophilization and discloses the amorphous form, which has unsuitable characteristics for large-scale production and has an unsuitable stability.

WO-A-97/49681 and its US equivalent US 6,124,340 describes that freeze drying of Fluvastatin Sodium yields a mixture of a crystalline form and amorphous material. The crystalline form comprised in this mixture is referred to as Fluvastatin Sodium form A. The estimated amount of Form A obtained by lyophilization as described in these patents is about 50%.

This patent describes a new crystalline form B preferably containing no more that 5% of any other crystalline form of Fluvastatin Sodium. The crystalline form B is precipitated

from a mixture of one or more organic solvents preferably polar organic solvents such as methanol or ethanol and water and isolated there from using polar organic solvent such as aliphatic alkanols, ketones and esters their of as precipitating solvent.

This patent describes the process in which any non-B form of Fluvastatin sodium amorphous material or fluvastatin sodium form A can initially be partly dissolved in the organic solvent and water mixture and stirred until the desired form B is formed.

The process comprises a transformation in the slurry without a complete dissolution of the starting material.

In second aspect, the patent discloses the crystallisation in an organic solvent and water, with a suitable sodium compound preferably an aqueous solution of sodium hydroxide or sodium carbonate. The starting material is eg. the corresponding free acid or the ester or a salt of fluvastatin.

In third aspect, the patent discloses the crystallisation from a solution of fluvastatin sodium in a mixture of organic solvent and water. The starting solution of fluvastatin sodium can be formed either by dissolution of already isolated fluvastatin sodium or it can be formed in a previous process step where fluvastatin sodium is formed by chemical reaction. The patent also describes that form B is less hygroscopic than fluvastatin sodium form A and amorphous fluvastatin sodium, improved stability against light exposure.

WO 02/36563 describes the crystalline forms of the (3R, 5S) – and the (3S, 5R) - enantiomers of fluvastatin sodium. The patent designated these forms as form A,

Form B1, Form B2, Form C, Form D and Form E. These crystalline forms are hydrates and have water contents from 0 upto 8 molecules of water per molecules of fluvastatin sodium. The patent disclose that form E can be prepared by treating an aqueous solution of the (3R, 5S) – or (3S, 5R)- enantiomers of fluvastatin sodium to precipitation either by concentrating or cooling followed by freeze drying of the suspension or of the precipitated compound. Form A, B, B_2, C and D are prepared by using form E as the starting compound and by exposing from E to an atmospheric having a defined relative humidity depending on the relative humidity used, the different forms can be obtained.

WO 03/013512 and its US equivalent US 2003032606 describes crystalline hydrates designated as form C, D, E and F with water content ranging from 3 to 32%. The patent also describes a new process for the preparation of highly crystalline Fluvastatin Sodium form A. The patent describes the process wherein Fluvastatin Sodium is exposed to an atmosphere having defined relative humidity to get form C, D, E and F. The patent further describes that these forms are less susceptible toward air humidity and show high stability and are easier to handle at normal environment humidity levels.

All these patents claim advantages over the existing patents in one way or the other. However, there is still a need for new crystalline forms which are more stable, easy to handle at normal environmental humidity level, highly pure with low level of residual solvents and high yield and having easily scale-up process.

The present invention provides a new crystalline form BA of Fluvastatin Sodium. This new crystalline form of Fluvastatin sodium is generally monohydrate with water content of 3 to 6% but also exhibits water content up to 8%.

Brief Description of the Drawing

Fig I depicts infrared spectra of new crystalline form BA of Fluvastatin sodium.

Fig II relates to powder x-ray diffraction (PXRD) pattern of new crystalline form BA of Fluvastatin sodium.

SUMMARY OF THE INVENTION:

The main object of the present invention is to provide to a novel crystalline polymorph of Fluvastatin sodium.

Another object is to provide a polymorph having higher purity, stability, and solubility.

Yet another object is to provide a polymorph having reduced residual solvent.

Still yet another object is to provide a polymorph that contains up to 8% preferably 3-6% water content.

One of the objects of the invention is also to provide a process, for the preparation of a novel polymorph.

The process is simple cost effective, involving less number of steps, high yielding, precise, reproducible, environment friendly easy to scale up for industrial manufacture without compromising the quality of the title product.

The process has merits of easy and rapid isolation and crystallization of stable polymorph containing residual solvent well below ICH limits.

We have surprisingly found out that the Fluvastatin sodium can be prepared as a novel crystalline hydrates which have improved stability, less hygroscopicity, without the risk of residual solvent, photostability by using ethers as precipitating solvent.

Summary of the Invention:

In a first aspect, the new crystalline form BA of Fluvastatin sodium is characterised by its infrared and powder x-ray diffraction pattern. Fourier transform infrared (FT – IR) spectra of Fluvastatin sodium were obtained from 4 mg of new crystalline form in 250 mg KBr, mortared and pressed into tablets.

The infrared spectrum of new crystalline form of Fluvastatin sodium form BA are expressed as cm^{-1} and the main peaks are 3412, 2977, 2936, 1586,1499, 1456, 1420, 1345, 1216, 1157, 1104, 1041, 1013, 969, 841, 740.

The powder x-ray diffractogram was performed on a Shimadzu XRD – 6000 with copper K radiation of $\lambda = 1.5406°A$ and pattern expressed in terms of the 2θ, d-spacing and relative intensities is shown in the following Table.

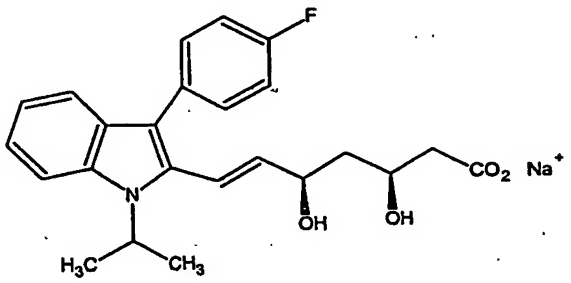
Table

2θ (± 0.2)	D (± 0.2)	Relative intensity (>15%)
03.97	22.19	100
11.08	07.97	26
12.06	07.33	94
12.92	06.84	90
14.92	05.93	24
15.79	05.60	56
16.54	05.35	18
17.78	04.98	56
18.32	04.83	56
18.84	04.70	49
19.64	04.51	60
20.42	04.34	63
21.58	04.11	61
22.46	03.95	29
23.98	03.70	21
24.26	03.66	20
25.56	03.48	48
26.30	03.38	34
26.92	03.30	17
28.64	03.11	33
29.82	02.99	15
30.80	**02.90**	**5**
32.19	02.77	18
33.12	**02.70**	**5**
35.00	**02.56**	**10**
36.08	**02.48**	**7**

36.52	02.45	9
36.94	02.43	13
37.66	02.38	4
39.78	02.26	6

The new crystalline form BA of Fluvastatin sodium is generally monohydrate with water contents in the range of 3 to 6 %. However, the hydrated form may exhibit water content up to 8.0%.

In a further aspect, the present invention provides a process for the preparation of new crystalline form BA of Fluvastatin sodium in hydrated state. R*, S*-(E) (±) 7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptanoicacid mono sodium salt having formula 1 is prepared using the following method.



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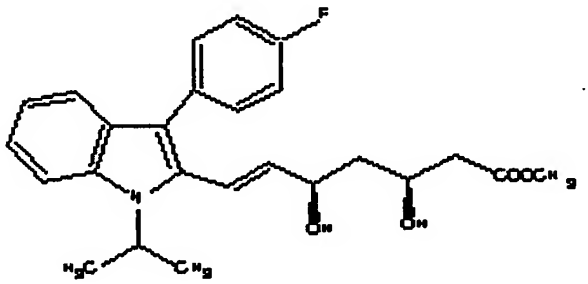
Accordingly the present invention provides a process for the preparation of a novel crystalline polymorph BA of Fluvastatin sodium comprising of the following steps:

(a) optionally converting methyl ester of Fluvastatin sodium having formula 2 to Fluvastatin sodium in an organic solvent using any known methods till reaction completion,

(b) providing clear solution of the said Fluvastatin sodium using water immiscible organic solvent exemplified without restriction, aliphatic alkanols,

(c) adding antisolvent such as ethers capable of facilitating precipitation and,

(d) isolating crystallised new polymorphic form BA of Fluvastatin Sodium.



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In an embodiment of the present invention the Fluvastatin sodium used may be amorphous or its any known form reported in prior art or mixture thereof in case step (a) involving conversion of methyl ester is not adopted. In a further embodiment, Fluvastatin sodium when used as a starting material may be in anhydrous or hydrated state.

In a still further embodiment an organic solvent used for converting methyl ester of Fluvastatin sodium may be selected from water immiscible organic solvent exemplified without restriction, aliphatic alkanols, aliphatic ketones or lower ethers.

In a further enbodiment the aliphatic alkanols used may be such as aliphatic branched or straight chain alkanols having 1 to 5 carbon atoms preferably methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol more preferably methanol.

In yet another embodiment the aliphatic ketones used may be the one having carbon atom up to 6 and may preferably be acetone. The ether when employed may be tetrahydrofuran (THF), dimethoxy ethane or dimethoxy propane.

The organic solvent used for converting methyl ester of Fluvastatin sodium may be 100 times preferably 10 times, more preferably 3.5 times of methyl ester of Fluvastatin sodium.

In yet another embodiment of the invention the organic solvent is completely recovered in case other than aliphatic alkanol is used for converting Fluvastatin methyl ester, and the residue thus produced is redissolved in alkanol to provide clear solution.

In an embodiment of the invention the methyl ester is converted to Fluvastatin sodium using aqueous solution of alkali metal hydroxide preferably sodium hydroxide.

In a further embodiment the aqueous solution of alkali metal hydroxide used may be 100 times preferably 1.0 times more preferably 0.25 times.

In a still further embodiment DM-water may be used during step (a) and may be 100 times preferably 1.0 times more preferably 0.25 times of the starting compound.

In a still further embodiment an organic solvent used for providing clear solution of Fluvastatin sodium may be selected from water immiscible organic solvent exemplified without restriction, aliphatic alkanols branched or straight chain, having 1 to 5 carbon atoms. The alkanols used may preferably be methanol, ethanol, 1-propanol,2-propanol, 1-butanol or 2-butanol, more preferably methanol.

In yet another embodiment, the organic solvent used for providing clear solution in step (b) may be 100 times preferably 15 times, more preferably 10 times of the Fluvastatin sodium or any form of Fluvastatin sodium used.

In another aspect of the invention, the organic solvent used for providing clear solution may be recovered by concentrating under vacuum to preferably 4.5 times of the source of Fluvastatin sodium

In a further embodiment, the clear solution may be obtained by heating to the reflux temperature of the solvent used preferably above 20°C & more preferably 30 to 40°C.

In another aspect of the invention, the anti solvent used for facilitating precipitation of new crystalline from of Fluvastatin sodium may be selected from aliphatic ethers. The aliphatic ethers used may be diethyl ether, di-isopropyl ether, methyl-t-butyl ether preferably di-isopropyl ether.

In a further embodiment the aliphatic ether used may be 100 times preferably 70 times more preferably 50 times of the starting compound.

In a still further embodiment, the addition of aliphatic ether, may be carried out at temperature between –10 to 80° C preferably 40-70° C more preferably 60-65°C.

In still another embodiment of this invention the seeding may be done in step (c) to accelerate precipitation. The seed may be used from the previous batch and added in the range of 1 to 10% w/w of the starting material.

The precipitation may be effected at 5°C to room temperature (about 25°C) when seeded.

In yet another embodiment stirring for precipitation of new crystalline form BA of Fluvastatin Sodium may be carried out up to 48 hrs. preferably for 24 hrs, more preferably 13-16 hrs.

The isolation may be effected by any conventional methods such as filtration either with pressure or vacuum, decantation, centrifugation. The drying may be effected, after step (d), by known means like vacuum tray drier, Rotacon vacuum drier and at a temperature above 50 and below 80°C preferably at 50-60°C for 12 to 48 hours to regulate the water of molecules.

One skilled in the art will appreciate that be adjusting the temperature and time for these steps one can optimize the yield of the desired product.

Detailed Description of the Invention:

Infrared spectra of new polymorphic crystalline form of Fluvastatin Sodium has 3412, 2977, 2936, 1586, 1499, 1456, 1420, 1345, 1216, 1157, 1104, 1041, 1013,969, 841, 740 cm^{-1}.

The IR spectra is well distinguished from that of IR spectra of known forms in the prior art. The vibrational frequencies (cm^{-1}) of new polymorphic form BA of Fluvastatin Sodium are shown in the accompanying figure 1.

IR shows absorption bands at 3409, 2976, 2937, 1587, 1535, 1499, 1458, 1420, 1347, 1216, 1156, 1105, 1041, 1013, 967, 841, 740 , 564 cm^{-1}

The powder x-ray diffractogram of new polymorphic crystalline form (Fig.2) displays peaks at 03.97± 0.2, 11.08± 0.2, 12.06± 0.2, 12.92± 0.2, 14.92± 0.2, 15.79± 0.2, 16.54± 0.2, 17.78± 0.2, 18.32± 0.2, 18.84± 0.2, 19.64± 0.2, 20.42± 0.2, 21.58± 0.2, 22.46± 0.2, 23.98± 0.2, 24.26± 0.2, 25.56± 0.2, 26.30± 0.2, 26.92± 0.2, 28.64± 0.2, 29.82± 0.2, 30.80± 0.2, 32.19± 0.2, 33.12± 0.2, 35.00± 0.2, 36.08± 0.2, 36.52± 0.2, 36.94± 0.2, 37.66± 0.2, 39.78 ± 0.2 degree 2θ.

The x-ray powder diffractogram of new polymorphic crystalline form BA (fig. II) has medium peaks at 11.14 ± 0.2, 12.45 ± 0.2, 14.70 ± 0.2, 15.72 ± 0.2, 22.50 ± 0.2, 23.98 ± 0.2, 25.56 ± 0.2, 26.84 ± 0.2, 28.55 ± 0.2, 29.76± 0.2, 32.04 ± 0.2 and large peaks at 17.88 ± 0.2, 19.46 ± 0.2, 20.10 ± 0.2, 21.52 ± 0.2 degree 2θ.

This x-ray pattern is well distinguished from that of known crystalline forms in prior art, which is characterised by sharp and strong peaks at 12.06, 12.92 degree 2θ, medium intensity sharp peaks at 18.32, 18.84, 19.64, 20.42, and medium intensity broad peaks at 21.58 and 25.56± 0.2 degree 2θ.

medium intensity sharp peaks at 18.32, 18.84, 19.64, 20.42, and medium intensity broad peaks at 21.58 and 25.56± 0.2 degree 2θ.

The x-ray powder diffractogram of fig. II was obtained by known methods using a Shimadzu XRD-6000. Copper radiation of $\lambda = 1.5406$ A° was used. Measurement range 3-40 degree 2θ. The 2θ, d-spacings and relative intensities with a relative intensity are indicated in the Table. X-ray powder diffraction is performed on ungrounded samples.

The new polymorphic form BA exists in hydrated form, generally monohydrate form. It contains up to 8.0% of water content.

The invention is further illustrated by the following examples, which should not construe the effective scope of the claims.

Example I.

To a stirred suspension of methyl ester of Fluvastatin (50.0 g) in methanol (175 ml) an aqueous solution of sodium hydroxide (5.0 g in 12.5 ml. DM-Water) was added. The reaction mixture was heated to 30-35°C and stirred at the same temperature till reaction was complete (monitored by TLC, methyl ester of Fluvastatin NMT 0.1%). The reaction mass was fine filtered to remove the suspended particles and di-isopropyl ether (2.5 Ltr.) was added slowly at 60-65°C. The reaction mass was stirred for 15 hrs. during which time new crystalline form BA of Fluvastatin sodium precipitated out. The product was filtered and then dried in vacuum tray drier at 50-60°C for 34- 36 hrs.

Yield = 47.75 g, Relative Purity (HPLC)= 99.51% AssayOAB (HPLC) 99.57% w/w. Water content (by K. F) =4.97% w/w. Residual Solvent(by Head Space GC) Methanol NMT 0.3%, Di-isopropyl ether NMT 0.3%

Example II.

Fluvastatin sodium (25.0 g) was added to a mixture of methanol (250) and DM water (7.0 ml) at room temperature and the mixture was heated for 30-45 minutes at 30 to 40°C to get clear solution. The clear solution was fine filtered to remove suspended particles and concentrated under vacuum at 35-40°C till 125 ml of the reaction volume was left. The reaction mass was heated to 60-65°C and di-isopropyl ether (1.25 lt) was added slowly at 60-65°C. The reaction mass was stirred for 15 hrs. at 60-65°C during which time new **crystalline form BA** of Fluvastatin sodium precipitated out. The product was filtered and then dried in vacuum tray drier at 50-60°C for34- 36 hrs.

Yield = 24.2 g, Relative Purity (HPLC)= 99.72% Assay, OAB (HPLC) 99.95 % w/w. Water content (by K. F) =4.86% w/w. Residual Solvent (by Head space GC) Methanol= NMT 0.3%, Di-isopropyl ether= NMT 0.3%

While the present invention has been described in term of its specific embodiment, certain modification and equivalent will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

ADVANTAGES

1. Novel crystalline polymorph of Fluvastatin Sodium having higher purity, stability, and solubility.
2. Polymorph having reduced residual solvent.
3. Polymorph that contains generally 4% , but may contain up to 8% water content.

5. The process is simple cost effective, involving less number of steps, high yielding, precise, reproducible, environment friendly easy to scale up for industrial manufacture without compromising the quality of the title product.
6. The process has merits of easy and rapid isolation and crystallization of stable polymorph.

CLAIMS:

We Claim:

1. A new crystalline form BA of Fluvastatin sodium having characterized by its powder x-ray diffraction pattern following 2θ values measured using Shimadzu XRD – 6000 with copper K radiation of λ = 1.5406°A and relative intensities >15%

03.97± 0.2, 11.08± 0.2, 12.06± 0.2, 12.92± 0.2, 14.92± 0.2, 15.79± 0.2, 16.54± 0.2, 17.78± 0.2, 18.32± 0.2, 18.84± 0.2, 19.64± 0.2, 20.42± 0.2, 21.58± 0.2, 22.46± 0.2, 23.98± 0.2, 24.26± 0.2, 25.56± 0.2, 26.30± 0.2, 26.92± 0.2, 28.64± 0.2, 29.82± 0.2, 30.80± 0.2, 32.19± 0.2, 33.12± 0.2, 35.00± 0.2, 36.08± 0.2, 36.52± 0.2, 36.94± 0.2, 37.66± 0.2 and 39.78 ± 0.2.

2. A new crystalline form BA of Fluvastatin sodium as claimed in claim 1 having characterized by its powder x-ray diffraction sharp and strong peaks at 12.06 and 12.92 degree 2θ.

3. A new crystalline form BA of Fluvastatin sodium as claimed in claim 1 having characterized by its powder x-ray diffraction medium peaks at 11.14 ± 0.2, 12.45 ± 0.2, 14.70 ± 0.2, 15.72 ± 0.2, 22.50 ± 0.2, 23.98 ± 0.2, 25.56 ± 0.2, 26.84 ± 0.2, 28.55 ± 0.2, 29.76± 0.2 and 32.04 ± 0.2.

4. A new crystalline form BA of Fluvastatin sodium as claimed in claim 1 having characterized by its powder x-ray diffraction large peaks at 17.88 ± 0.2, 19.46 ± 0.2, 20.10 ± 0.2 and 21.52 ± 0.2 degree 2θ.

5. A new crystalline form BA of Fluvastatin sodium as claimed in claim 1 having characterized by its powder x-ray diffraction medium intensity sharp peaks at 18.32, 18.84, 19.64 and 20.42 ± 0.2 degree 2θ.

6. A new crystalline form BA of Fluvastatin sodium as claimed in claim 1 having characterised by its powder x-ray diffraction medium intensity broad peaks at 21.58 and 25.56± 0.2 degree 2θ.

7. A new crystalline form BA of Fluvastatin sodium as claimed in claim 1 having characterised by Infra Red Spectra expressed as cm^{-1} by main peaks at 3412, 2977, 2936, 1586,1499, 1456, 1420, 1345, 1216, 1157, 1104, 1041, 1013,, 969, 841, 740.

8. A new crystalline form BA of Fluvastatin sodium as claimed in claim 1 having characterised by IR bands at 3409, 2976, 2937, 1587, 1535, 1499, 1458,,1420, 1347, 1216, 1156, 1105, 1041, 1013, 967, 841, 740 and 564 cm^{-1}

9. A new crystalline form BA of Fluvastatin sodium as claimed in claim 1 contains up to 8% water content.

10. A new crystalline form BA of Fluvastatin sodium as claimed in claim 1 is monohydrate (about 4% water content)

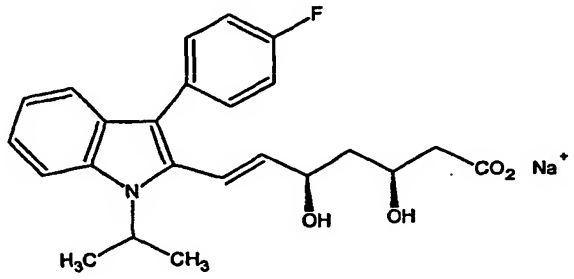
11. A process for the preparation of a novel crystalline polymorph BA of Fluvastatin sodium having formula 1 comprising of the following steps:

(b) optionally converting methyl ester of Fluvastatin sodium having formula 2 to Fluvastatin sodium in an organic solvent using any known methods till reaction completion,

(b) providing clear solution of the said Fluvastatin sodium using water immiscible organic solvent exemplified without restriction, aliphatic alkanols,

(c) adding antisolvent such as ethers capable of facilitating precipitation and,

(d) isolating crystallised new polymorphic form BA of Fluvastatin Sodium.



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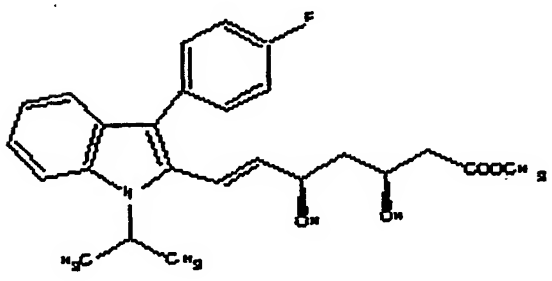

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12. A process as claimed in claim 11 wherein the Fluvastatin sodium used is amorphous or its any known form reported in prior art or mixture thereof in case step (a) involving conversion of methyl ester is not adopted.

13. A process as claimed in claims 11and 12 wherein the Fluvastatin sodium when used as a starting material is in anhydrous or hydrated state.

14. A process as claimed in claim 11 wherein the organic solvent used for converting methyl ester of Fluvastatin sodium is selected from water immiscible organic solvent exemplified without restriction, aliphatic alkanols, aliphatic ketones or lower ethers.

15. A process as claimed in claims 11 and 14 wherein the aliphatic alkanols used are aliphatic branched or straight chain alkanols having 1 to 5 carbon atoms preferably methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol more preferably methanol.

16. A process as claimed in claims 11 and 14 wherein the aliphatic ketones used are the one having carbon atom up to 6 and may preferably be acetone.

17. A process as claimed in claims 11 and 14 wherein the lower ether are selected from tetrahydrofuran (THF), dimethoxy ethane or dimethoxy propane.

18. A process as claimed in claims 11 to 18 wherein the organic solvent used for converting methyl ester of Fluvastatin sodium are 100 times preferably 10 times, more preferably 3.5 times of methyl ester of Fluvastatin sodium.

19. A process as claimed in claims 11 to 18 wherein the organic solvent is completely recovered in case other than aliphatic alkanol is used for converting Fluvastatin methyl ester, and the residue thus produced is redissolved in alkanol to provide clear solution.

20. A process as claimed in claims 11 the methyl ester is converted to Fluvastatin sodium using aqueous solution of alkali metal hydroxide preferably sodium hydroxide.

21. A process as claimed in claims 11 and 20 wherein the aqueous solution of alkali metal hydroxide used is 100 times preferably 1.0 times more preferably 0.25 times.

22. A process as claimed in claims 11 wherein the DM-water is used during step (a) and/or (b) is 100 times preferably 1.0 times more preferably 0.25 times of the starting compound.

23. A process as claimed in claims 11wherein the organic solvent used for providing clear solution of Fluvastatin sodium is selected from water immiscible organic solvent exemplified without restriction, aliphatic alkanols branched or straight chain, having 1 to 5 carbon atoms.

24. A process as claimed in claims 11 and 23 wherein the alkanols used are methanol, ethanol, 1-propanol, 2-propanol, 1-butanol or 2-butanol, preferably methanol.

25. A process as claimed in claims 11 and 23, 24 wherein the organic solvent used for providing clear solution in step (b) is 100 times preferably 15 times, more preferably 10 times of the Fluvastatin sodium or any form of Fluvastatin sodium used.

26. A process as claimed in claims 11 and 23 to 25 wherein the organic solvent used for providing clear solution is recovered by concentrating under vacuum to preferably 4.5 times of the source of Fluvastatin sodium.

27. A process as claimed in claims 11 and 23 -26 wherein the clear solution is obtained by heating to reflux temperature of the solvent used preferably above 20°C & more preferably 30 to 40°C.

28. A process as claimed in claims 11 wherein the anti solvent used for facilitating precipitation of new crystalline from of Fluvastatin sodium is selected from aliphatic ethers.

29. A process as claimed in claims 11 and 28 wherein the aliphatic ethers used is diethyl ether, di-isopropyl ether, methyl-t-butyl ether preferably di-isopropyl ether.

30. A process as claimed in claims 11 and 28-29 wherein the aliphatic ether used is 100 times preferably 70 times more preferably 50 times of the starting compound.

31. A process as claimed in claims 11 and 28-30 wherein the addition of aliphatic ether, is carried out at temperature between –10 to 80° C preferably 40-70° C more preferably 60-65°C.

32. A process as claimed in claims 11 wherein the seeding is done in step (c) to accelerate precipitation.

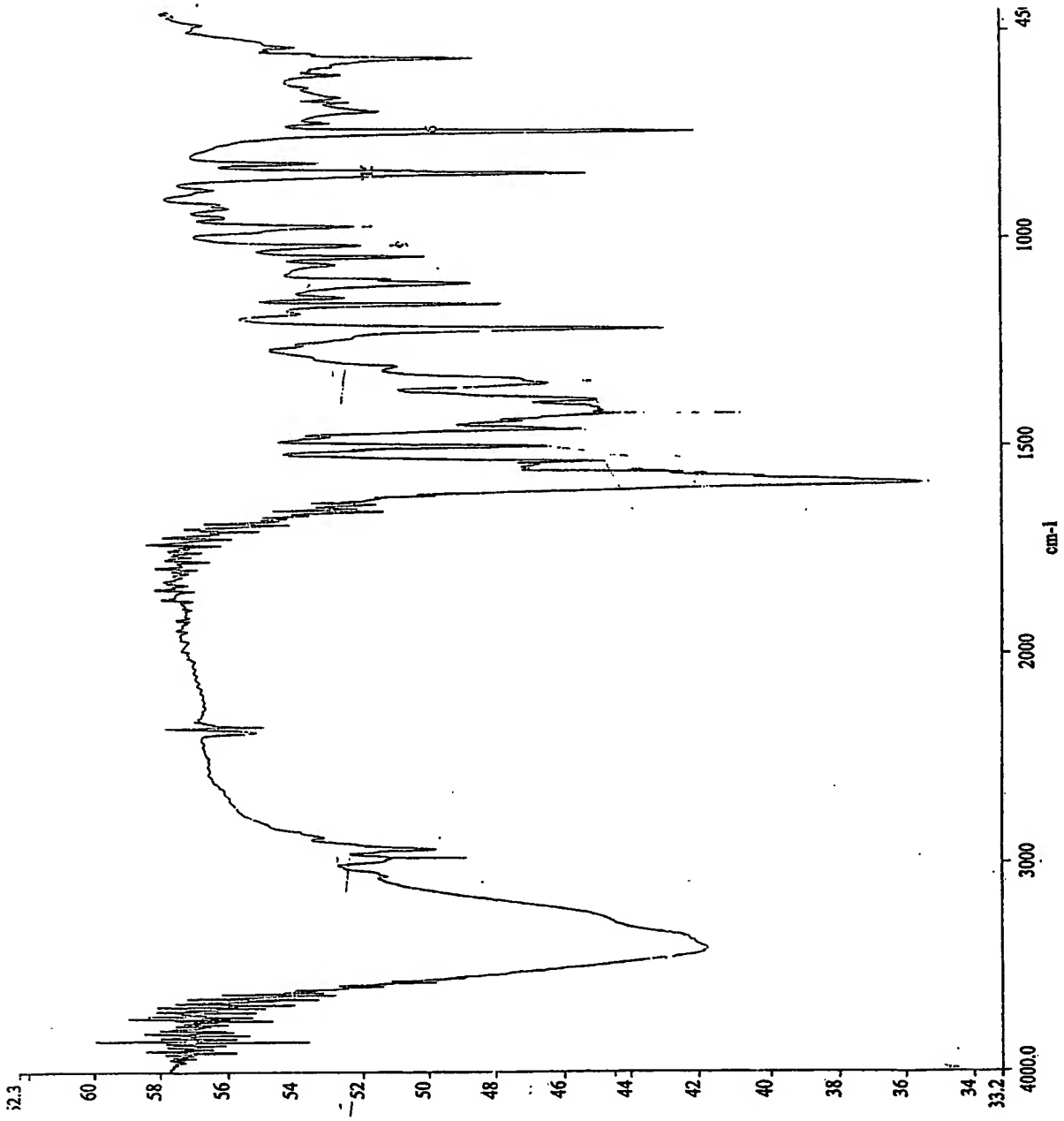
33. A process as claimed in claims 11 and 32 wherein the seed is used from the previous batch and added in the range of 1 to 10% w/w of the starting material.

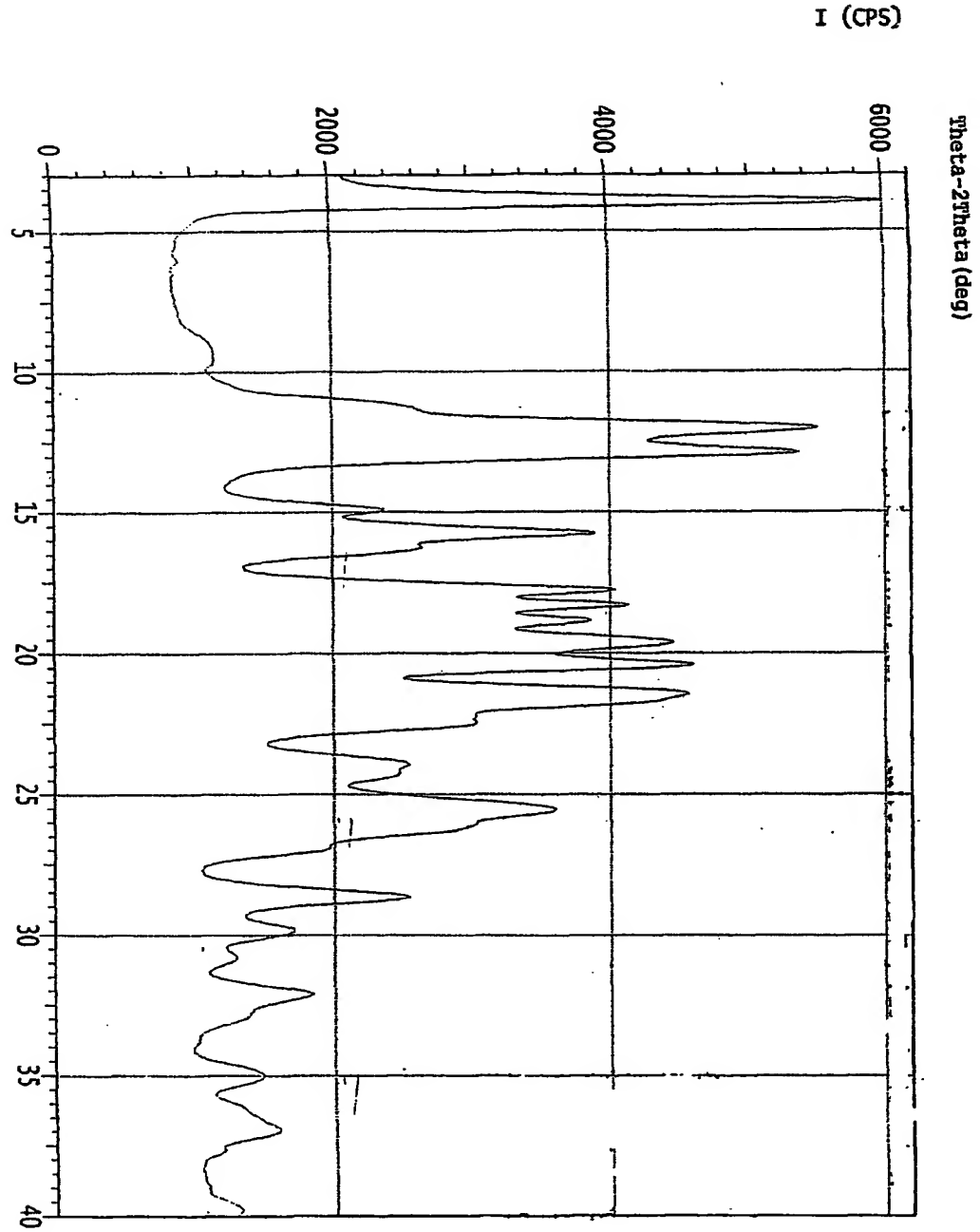
34. A process as claimed in claims 11 and 32-33 wherein the precipitation is effected at 5°C to room temperature (about 25°C) when seeding is done.

35. A process as claimed in claims 11 wherein the precipitation is carried out under stirring up to 48 hrs. preferably for 24 hrs, more preferably 13-16 hrs.

36. A process as claimed in claims 11 wherein the isolation is effected by any conventional methods such as filtration either with pressure or vacuum, decantation, centrifugation.

37. A process as claimed in claims 11 wherein the drying is effected, after step (d), by known means like vacuum tray drier, Rotacon vacuum drier and at a temperature above 50 and below 80°C preferably at 50-60°C for 12 to 48 hours to regulate the water of molecules.





(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 November 2004 (11.11.2004)

PCT

(10) International Publication Number
WO 2004/096765 A3

(51) International Patent Classification[7]: C07D 209/24, A61K 31/405

(21) International Application Number: PCT/IN2004/000121

(22) International Filing Date: 30 April 2004 (30.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
656/DEL/2003 1 May 2003 (01.05.2003) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
27 January 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A NOVEL CRYSTALLINE POLYMORPH OF FLUVASTATIN SODIUM AND A PROCESS FOR PREPARING IT

(57) Abstract: This invention relates to a novel crystalline polymorphic form BA of Fluvastatin Sodium and hydrates thereof, characterized by its IR and PXRD analysis. The invention also provides a process for the preparation of the novel polymorph that involves use of aliphatic ethers as antisolvent to facilitate precipitating. Further the addition of antisolvent is preferably carried out at a temperature above 40°C in the absence of seeding.

WO 2004/096765 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN2004/000121

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/24 A61K31/405

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of the actual completion of the international search	Date of mailing of the international search report
26 October 2004	08/11/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	vanVoorsttotVoorst,M

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INTERNATIONAL SEARCH REPORT

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